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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,257	02/14/2002	Chih-Pin Liu	1954-313	5061

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
VANDERVEGT, FRANCOIS P	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,257	LIU ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2004 and 16 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 36-48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06182002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/268,714.

Claims 1-48 are currently pending.

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-35, in the reply filed on May 6, 2004 is acknowledged. The traversal is on the ground(s) that the method claims of Group II are all dependent upon the composition claims of Group I and therefore contain the same limitations. This is not found persuasive because the composition of Group I can be used independently of the method of Group II, for example for the production of antibodies to the MHC/peptide complex or for isolating a specific population of T cells from a mixed population.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's election without traverse of the species of antigenic peptides related to diabetes in the reply filed on May 6, 2004 and confirmed in the reply filed August 16, 2004 is acknowledged.

3. **Claims 36-48 are withdrawn** from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 6, 2004.

Claims 6 and 7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on May 6, 2004.

Claims 1-5 and 8-35 are the subject of examination in the present Office Action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4, 17, 18, 23 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892).

Z'hu teaches a nucleic acid encoding a recombinant single-chain human MHC class II molecule (HLA-DR1) comprising an antigenic peptide covalently bound via a linker to the extracellular domain of the MHC class II beta chain. The linker allows the MHC class II molecule to properly fold and present the antigenic peptide (page 1934, second column in particular). Z'hu teaches that the nucleic acid encoding the beta chain and peptide was truncated to delete the transmembrane domain of the beta chain and attached to a nucleic acid encoding the extracellular domain of MHC class II alpha chain and then the insertion of a truncation signal to delete the transmembrane domain of the alpha chain (second column of page 1934, page 1935 and Figure 1 in particular). The prior art teaching anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-5, 8-12, 17-23, 26-29 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002).

Z'hu has been discussed supra.

Z'hu does not teach glutamic acid decarboxylase (GAD) peptides in association with MHC class II molecules.

Chao teaches the identification of peptide epitopes from GAD 65 that bind to a murine MHC class II haplotype that is associated with diabetogenesis in non-obese diabetic (NOD) mice (A^{g7}) (second column of page 29, Table 2 and Figure 2 in particular). Chao teaches that 63% of GAD reactive T cell hybridomas in the study reacted with peptide 206-220 of GAD 65, which is the same peptide as the

instantly disclosed and claimed SEQ ID NO: 1 (column 1 of page 32, Table 2 and Figure 2 in particular). Chao further teaches that peptide 524-543 is a major immunogenic epitope of GAD 65 (Figure 3 in particular), which is the same peptide as the instantly disclosed and claimed SEQ ID NO: 2.

Chao teaches that the human MHC class II HLA-DRB1*0405 haplotype is a susceptibility allele for insulin-dependent diabetes mellitus (IDDM) and is structurally related to the murine A^{g7} haplotype of NOD mice (page 33, column 1 in particular). Chao teaches that SEQ ID NO: 1 does not completely fit the predicted motif for binding to HLA-DRB1*0405 or to A^{g7}. Chao teaches that this id not unusual, however, as predicted motifs are based upon peptide elution and therefore select for abundant peptides, which are not necessarily the most immunogenic peptides (page 33, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to use the guidance of the teachings of Z'hu to construct nucleic acid molecules encoding soluble single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to the GAD 65 antigenic peptide of SEQ ID NO: 1. The artisan would have been motivated to combine the teachings with a reasonable expectation of success in order to examine the suggestion of Chao that HLA-DRB1*0405 may present the GAD 65 206-220 peptide to T cells in IDDM patients in light of the teaching of Z'hu that the unique properties of such engineered HLA molecules can facilitate an understanding of the nature of antigen recognition (Abstract in particular).

6. Claims 1-5, 8-13, 15, 17-24, 26-30 and 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002) and Crawford et al (Immunity [1998] 8:675-682; cited on form PTO-1449 filed June 18, 2002).

Z'hu and Chao have been discussed supra.

The combined references do not teach labeling of the soluble MHC molecule with biotin.

Crawford teaches the biotinylation of soluble MHC class II molecules (see entire report, page 680, column 1 in particular). Crawford further teaches attachment of phycoerythrin/streptavidin complexes to the biotinylated soluble MHC class II/peptide complexes to create a stable multimeric molecular complex (page 680, column 1 in particular).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Z'hu and Chao with the teachings of Crawford to create multimeric MHC class II complexes comprising GAD 65 peptide antigens. The artisan would have been motivated to combine the teachings with a reasonable expectation of success to create to create soluble

single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to GAD 65 antigenic peptides by combining the teachings of Z'hu and Chao as set forth supra and make stable multivalent complexes by way of biotinylation in the manner of Crawford because Crawford teaches that monomeric soluble MHC class II molecules have affinities too low for reliably detecting antigen-specific T cells, while multimeric MHC class II complexes have increased avidity for T cells due to the cooperative effect of multipoint binding (page 679, column 1 in particular).

7. Claims 1-5, 8-12, 14, 16-23, 25-29, 31 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Z'hu et al (Eur. J. Immunol. [1997] 27:1933-1941; U on form PTO-892) in view of Chao et al (Immunogenetics [1997] 46:29-34; cited on form PTO-1449 filed June 18, 2002) and U.S. Patent No. 6,232,445 to Rhode et al (patent date May, 15, 2001, filed October 29, 1997; A on form PTO-892).

Z'hu and Chao have been discussed supra.

The combined references do not teach oligohistidine tags.

The '445 patent further teaches that recombinantly produced soluble MHC molecules can be engineered to comprises a tail or "tag," such as oligohistidine (6x-His) that can be used for purification [claims 9 and 10] (column 27, lines 8-20 and column 54, lines 59-64).

It would have been prima facie obvious to a person having ordinary skill in the art at the time the invention was made to combine the teachings of Z'hu and Chao with the teachings of the '445 patent to create MHC class II complexes comprising GAD 65 peptide antigens and bearing an oligohistidine tag. The artisan would have been motivated to combine the teachings with a reasonable expectation of success to create to create soluble single-chain MHC class II molecules of human HLA-DRB1*0405 covalently bound to GAD 65 antigenic peptides by combining the teachings of Z'hu and Chao as set forth supra and tagging the molecules by incorporating an oligohistidine tail as taught by the '445 patent in order to simplify the purification of the recombinantly produced molecules from culture medium.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

F. Pierre VanderVegt, Ph.D.
Patent Examiner
October 21, 2004

PATRICK J. NOLAN, PH.D.
PRIMARY EXAMINER
10/26/04